## REMARKS

The Office Action dated September 14, 2010 has been reviewed and the comments of the U.S. Patent and Trademark Office have been considered. Applicant offers this amendment in response.

**Status of the Claims**

Claims 15-16 and 19-23 are pending and under consideration. Claim 15 is currently amended, with support specifically found at Page 4, lines 23-26 and at Page 6, line 28 through Page 7, line 2; and generally throughout the specification and claims as originally filed.

**Rejection under 35 U.S.C. § 112 – First Paragraph – New Matter**

The Office rejects claims 15-16 and 19-23 for allegedly introducing new matter. Applicant respectfully traverses.

The Office alleges the specification does not support the phrase: "wherein said lipidic phase is not a product of reverse-phase evaporation." The Office alleges that this is new matter. Applicant respectfully traverses.

Negative limitations having basis in the original disclosure are acceptable for claim language. "So long as the boundaries of the patent protection sought are set forth definitively, albeit negatively, the claim complies with the requirements of 35 U.S.C. 112, second paragraph." MPEP § 2173.05(i).

In the present application and pending claims, the claimed invention meets all requirement of 35 U.S.C. 112, second paragraph. The methods by which the liposomes and lipidic phase are formed are definitively delineated in the original specification. See Specification at Page 4, lines 6-26; more specifically at Page 7, line 25 through Page 8, line 8;

for example. Consequently, there is no ambiguity as to how the liposomes and lipidic phase are formed in the presently claimed invention.

The original Specification provides a basis for the negative provision regarding reverse-phase evaporation methods. The original Specification specifically teaches the unwanted aspects of reverse-phase evaporation as it relates to liposomal formulations. See Specification at Page 2, line 29 through Page 3, line 12. As is clear and unambiguous to the skilled artisan, these aspects of the reverse-phase evaporation methodology are not part of the methodology for making the liposomes and lipidic phase of the claimed invention.

Therefore, the original disclosure is clear and unambiguous as to how the liposomes and lipidic phase are formed in the current invention. Furthermore, the original disclosure is clear and unambiguous that reverse-phase evaporation has particular characteristics that are not desired in the presently disclosed invention. Consequently, the original disclosure provides the basis for the negative limitation of the presently claimed invention regarding the phrase "wherein said lipidic phase is not a product of reverse-phase evaporation." For these reasons, Applicant respectfully requests that the rejection be withdrawn.

**Rejection under 35 U.S.C. § 112 – Second Paragraph**

The Office rejects claims 15-22 for allegedly being indefinite regarding the recitation: "active ingredient being dispersed within the aqueous phase and not within the liposome of the lipidic phase." Applicant respectfully traverses.

Applicant wishes to note that claims 17-18 were previously canceled. Therefore, Applicant believes the rejection was over 15-16 and 19-22, and the following comments are based on the subject matter of claims 15-16 and 19-22.

Without acquiescing to the merits of the rejection, Applicant has amended claim 15 to recite: "active ingredient being dispersed within the aqueous phase outside of the liposomes of the lipidic phase." This phrase is also supported in the original disclosure at Page 4, lines 23-26; and Page 6, line 28 through Page 7, line 2. Consequently, there is no ambiguity that the active agent is in the aqueous phase outside of the liposomes of the lipidic phase. For these reasons, Applicant respectfully requests that the rejection be withdrawn.

**Rejection under 35 U.S.C. § 103(a)**

The Office rejects claims 15-16 and 19-23 for allegedly being unpatentable over either JP 08 231417 ("'JP 417") or Maitani by themselves in view of JP 61097229 ("'JP229"); or JP417 in view of U.S. Patent 5,874,075 ("Collins") and further in view of JP229, of which all are of record. Applicant respectfully traverses.

The cited references, alone or in combination, do not meet all the requirements of the claimed invention.

*Itemized Deficiencies of Each Reference; JP417, Maitani and JP229 Combination*

JP417 forms liposomes and the lipidic phase by reverse-phase evaporation, which encapsulates the active ingredient. The present invention uses liposomes and lipidic phase formed by methodology different from reverse-phase evaporation. Also, the present invention

specifically requires that the EPO, the active ingredient, be in the aqueous phase outside the liposomes of the lipidic phase. JP417 does not teach any of these aspects of the present invention. In fact, JP417 teaches away from the claimed invention wherein JP417 drives encapsulation of active ingredient through reverse-phase evaporation. Therefore JP417 would not lead one of ordinary skill in the art to the present invention because one of ordinary skill in the art would view JP417 for what it teaches, which is encapsulation of the active agent through reverse-phase evaporation.

Maitani, like JP417, teach reverse-phase evaporation techniques to drive encapsulation of the active ingredient. As discussed above for JP417, this teaches away from the present invention, wherein the present invention does not encapsulate the EPO. The present invention uses methodology that keeps the EPO in the aqueous phase outside the liposomes of the lipidic phase. Moreover, Maitani, like JP417, removes the non-encapsulated EPO; a further teaching away from the present invention. Since the purpose and teaching of Maitani is to encapsulate the active ingredient, there would be no reason for one of ordinary skill in the art to modify the process to achieve the presently claimed invention. Moreover, the Office has not proffered any rationale as to why one of ordinary skill in the art would go counter to the encapsulation teachings of Maitani. Maitani simply teaches a different invention with techniques not in the present invention to obtain compositions that are not in the present invention.

JP229 does not teach liposomal dispersions at all. There is no teaching in JP229 that would allow one of ordinary skill to cure the deficiencies of JP417 and Maitani with reverse-phase evaporation. Therefore, all three of these references fail to offer any guidance as to how one of ordinary skill could: 1) avoid encapsulation of the active ingredient by liposomes formed with reverse-phase evaporation; 2) keep only active ingredient that is outside the liposomes formed with reverse-phase evaporation. There is no way to combine these references to overcome the teaching away of JP417 and Maitani's encapsulation with liposomes made from reverse-phase evaporation.

Therefore, JP417, Maitani and JP229 do not teach or suggest all the requirements of the presently claimed invention, wherein neither reference teaches liposomes and lipidic phase formed without reverse-phase evaporation techniques, and wherein neither reference teaches the active ingredient outside the liposomes of the lipidic phase. For these reasons, the Office has failed to establish a basis for a *prima facie* case of obviousness, and the rejection should be withdrawn. Applicant respectfully requests that the claims be allowed to proceed to issuance.

*Itemized Deficiencies of Each Reference: JP417, Collins and JP229 Combination*

JP417 suffers the deficiencies discussed *supra*, which apply to this combination by the Office.

Collins fails to cure the deficiencies of JP417. By relying on Collins' broad disclosure, the Office is picking and choosing from a broad genus of compounds, and is inviting experimentation by one of ordinary skill in the art with no reasonable expectation of success.

*i) Arguments in Response to the Office's Assertions Regarding Collins*

As stated in the previous response, Collins teaches a broad genus of compounds that are incorporated into the structure of the liposome via complex bonding/bridging via very specific modifications (Col. 8, lines 8-25, for example). The Office now alleges that Example 1 of Collins teaches "mixing of hematopoietic factor itself (G-CSF) and not modified G-CSF." The Office's reading of Example 1 in Collins is in error. Example 1 specifically states:

> "The G-CSF:phospholipid complexes were prepared by mixing **G-CSF (as described above)** with a particular lipid (as described above)." *emphasis added*

The "*G-CSF (as described above)*" definitively refers to the specifically modified G-CSF as described, for example, at Col. 8, lines 8-25 and Col. 13, lines 5-19. Contrary to the Office's interpretation and application of Collins, the present invention does not teach modifications to the EPO that would permit the bonding/bridging of select compounds for incorporation of the EPO into the membrane of the liposomes via the incubation step of Collins. To this point, the Office's assertion that the incubation step of Collins would necessarily result in the same product as the currently claimed invention is without merit in light of the above discussion regarding the required modifications taught by Collins.

Moreover, the presently claimed invention teaches the EPO as being "dispersed with the aqueous phase outside of the liposome of the lipidic phase." Collins does not teach this and does not combine with any other reference to teach the claimed invention.

*ii) Previous Arguments Against Collins Maintained*

Collins fails to teach EPO being dispersed within the aqueous phase and not within a liposome of the lipidic phase as presently claimed. Collins does not specifically teach EPO as part of any specific liposomal-based parenteral composition. Moreover, Collins mentions EPO as part of a larger group of compounds that could be considered for use in the Collins invention requiring various modifications for incorporation into the liposome membrane. Collins does not provide any guidance regarding the use of EPO in the methods of Collins. Collins does not specifically claim or provide examples regarding EPO. Collins brief mentioning of EPO as a member of a larger group of compounds is nothing more than an invitation to experiment. There is simply a lack of information in Collins to offer one of ordinary skill the ability to practice Collins as to EPO.

Collins requires very specific modifications for bonding/bridging select compounds to incorporate those select compounds into the membrane of the liposomes. This requires particular protein modifications discussed in Collins (Col. 8, ll. 8-25, for example); however, Collins does not offer any insight as how to perform these potential modifications to incorporate EPO into the membrane of the specific liposomes or lipid complexes disclosed in Collins. The Office is requiring one of ordinary skill to pick and choose from a large genus of compounds, including EPO, to combine Collins with any other reference to achieve the presently claimed invention.

Contrary to the Office's assertion, this does not meet the burden of establishing a *prima facie* case of obviousness.

As admitted by the Office and taught in Collins, G-CSF is incorporated into the membrane of the lipid structure and is not dispersed in the aqueous phase as presently claimed. The Office's assertion that membrane-bound G-CSF is equivalent to the claimed EPO being dispersed in the aqueous phase is unsubstantiated and appears to be counter to the teachings of Collins.

Collins does not teach dispersal of G-CSF in the aqueous phase but does teach incorporation of the G-CSF into the membrane. One of ordinary skill in the art would not look to Collins as teaching dispersal within the aqueous phase but would reasonably read Collins as requiring a level of chemical modification to specifically incorporate the G-CSF into the lipid membrane. One of ordinary skill in the art would read Collins as lacking any specific teachings regarding EPO being dispersed in an aqueous phase.

Despite the fact that Collins does not provide any specific guidance regarding most of the compounds mentioned in the large genus of contemplated compounds, the Office asserts that Collins teaches the compounds incubated with the liposomes "with an aqueous solution of the protein and if EPO attaches to the liposomal surface by some interaction, then EPO would behave the same way in instant invention also." Office Action Page 5. First and foremost, the Office offers no scientific rationale regarding this point.

Second, Example 1 (Col. 14, ll. 1-17) definitively shows the steps taken to drive attachment and/or incorporation of G-CSF into the liposomal membrane, and this is achieved by

the modified G-CSF for bonding/bridging as described in the passages leading up to Example 1 in Collins. There is no mention of EPO and there is no evidence that this occurs merely by incubation of the liposome with the protein solution as proposed by the Office. This is a baseless interpretation by the Office.

JP229 reference does not teach a liposomal-based parenteral composition. The JP229 reference does not teach an aqueous phase, buffer solution and a lipidic phase. Moreover, the JP229 reference does not teach EPO dispersed in the aqueous phase and not within a liposome of the lipidic phase.

For these reasons and the reasons stated above, JP417, Collins and JP229 cannot be combined to achieve the presently claimed invention. Therefore, the Office has failed to establish the basis for a *prima facie* case of obviousness, and Applicant respectfully requests that the rejection be withdrawn.

*Itemized Deficiencies of Each Reference: Collins and JP229 Combination*

The Office rejects claims 15-16 and 19-23 as allegedly being unpatentable over Collins in view of JP229. Applicant respectfully traverses.

As discussed above, Collins teaches a broad genus of compounds with little to know guidance regarding members of the genus except for G-CSF. The Office is merely picking and choosing from a broad genus of compounds in an attempt to anticipate the presently claimed

invention. Furthermore, Collins teaches methods of incorporating G-CSF in the membrane of the liposome through modification to the G-CSF that allows for bonding/bridging with the liposome membrane during incubation. One of ordinary skill in the art would not look to Collins membrane incorporated, modified G-CSF/liposome complexes for achieving the presently claimed invention. Moreover, one of ordinary skill in the art would not be able to cure the deficiencies of Collins by looking to JP229, because JP229 does not teach a liposomal-based dispersion as presently claimed.

For these reasons, the Office has failed to establish a *prima facie* case of obviousness, and the rejection should be withdrawn. Applicant respectfully requests that the claims be allowed to proceed to issuance.

## CONCLUSION

In view of the above amendment, Applicant believes the pending application is in condition for allowance and requests favorable action on the merits. Should the Office feel that any issues remain, Applicant requests that the Office contact the undersigned so that the issues may be expeditiously addressed and prosecution of the instant application continued.

Applicant submits concurrently a Request for Continued Examination pursuant to 37 C.F.R. § 1.114. Please charge our Credit Card in the amount of $810 covering the fees set forth in 37 C.F.R. § 1.17(e). In the event any extensions of time are necessary to prevent the abandonment of this patent application, then such extensions of time are petitioned. The U.S. Patent and Trademark Office is authorized to charge any additional fees that may be required in

conjunction with this submission to Deposit Account Number 50-2228, under Order No. 026038.0240N1US from which the undersigned is authorized to draw.

Dated: December 14, 2010

Respectfully submitted,

By 

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